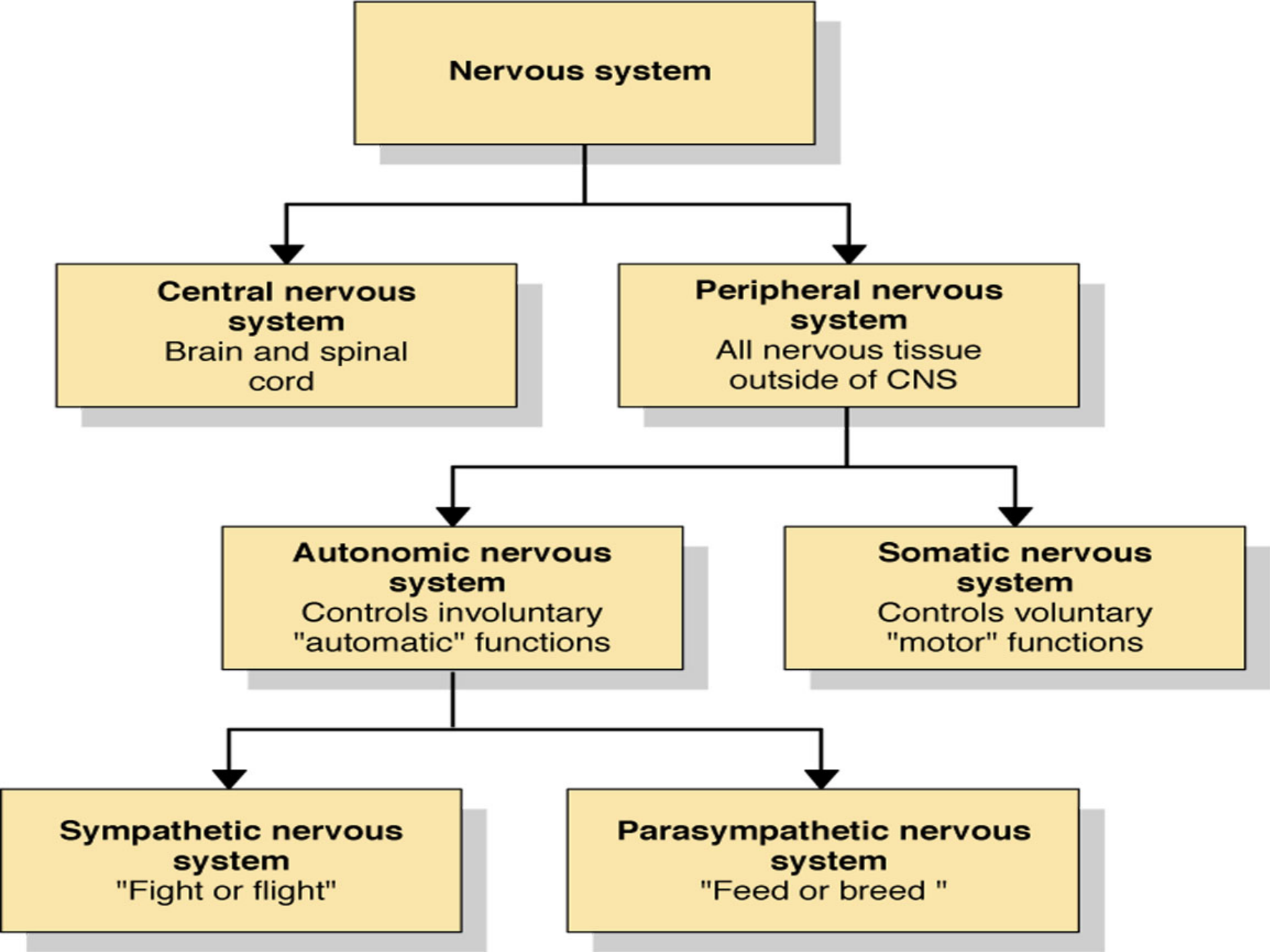
Drugs used to affect the Nervous system

- Many pathological conditions involve the central nervous system (CNS).
- As a result, many drugs have been developed to affect the CNS.


Nervous system
Central nervous system
Brain and spinal cord
Peripheral nervous system
All nervous tissue outside of CNS
Autonomic nervous system
Controls involuntary "automatic" functions
Somatic nervous system
Controls voluntary "motor" functions
Sympathetic nervous system
"Fight or flight"
Parasympathetic nervous system
"Feed or breed "

Autonomic Division of the Peripheral Nervous System

The heart, many glands, and smooth muscles are innervated by both sympathetic and parasympathetic nerve fibers

Cholinergic and Adrenergic Fibers

Acetylcholine (Cholinergic)

- The neurotransmitter for the ganglionic synapse between preganglionic and postganglionic fibers of the sympathetic and parasympathetic divisions
- The neurotransmitter at the junction between the parasympathetic postganglionic fiber and the effector cell

Acetylcholine (Cholinergic) (cont.)

- Fibers that release acetylcholine are known as cholinergic fibers.
- All preganglionic neurons of the sympathetic division and all postganglionic neurons of the parasympathetic division are cholinergic

Norepinephrine (Adrenergic)

- The neurotransmitter between the sympathetic postganglionic fiber and the effector cell.
- Fibers that release norepinephrine are adrenergic fibers
- Most postganglionic neurons of the sympathetic division are adrenergic

The **sympathetic** system dominates during stressful events. i.e.: **Fight or Flight**, or fright syndrome

The **parasympathetic** system is most active during periods of emotional and physical calm; **Feed or Breed**

Drugs Affecting the Cardiovascular System

Pharmacological Terms to Describe Actions of Cardiovascular Drugs

- Chronotropic drugs
  - Affect heart rate
  - A drug that **accelerates heart rate** is said to have a positive chronotropic effect (**isoproterenol**)
  - A drug that decreases the heart rate is said to have a negative chronotropic effect (verapamil)

Pharmacological Terms to Describe Actions of Cardiovascular Drugs (cont.)

- Dromotropic drugs
  - Affect conduction velocity through the conducting tissues of the heart
  - If a drug speeds conduction, it is said to have a positive dromotropic effect (isoproterenol)
  - If a drug slows conduction, it is said to have a negative dromotropic effect (adenosine)

Pharmacological Terms to Describe Actions of Cardiovascular Drugs (cont.)

- Inotropic drugs
  - Affects force of contraction
  - A drug that strengthens or increases the force of contraction is said to have a positive inotropic effect (epinephrine)
  - A drug that weakens or decreases the force of contraction is said to have a negative inotropic effect (propranolol)

Review of Cardiac Anatomy

- Essentially a two sided pump
  - Right side is a low pressure.
  - Left side is a high pressure
- Cardiac Output
  - Determined by Stroke Volume and Heart Rate
  - The “Atrial Kick” can increase cardiac output by up to 25%

Cardiovascular Physiology Review

- Impulse generation and conduction
  - The heart is composed of many interconnected branching fibers or cells that form the walls of the two atria and two ventricles.
  - Some cells are specialized to conduct electrical impulses

Cardiovascular Physiology Review (cont.)

- Some have contraction as their primary function.
- Cardiac drugs are classified by their effects on these tissues

Depolarization

- The process of eliminating or reversing the charge across a cell membrane

Fast action potential

- Found in cardiac muscle tissue
- Cyclic activity has five phases

Fast action potential (cont.)

- Phase 0
  - Represents depolarization.
  - Results from rapid influx of Na+ ions causing the inside of the cell to become more positive.
  - Normally caused by the arrival of an impulse generated somewhere else in the heart.

Fast action potential (cont.)

- Phase 1
  - K+ begins to leave the cell.
  - Returning the cell to its normal negative charge

Fast action potential (cont.)

- Phase 2
  - Interrupts Phase 1 with an influx of Ca++ into the cell.
  - AKA the Plateau phase.
  - Delays repolarization.
  - Important for medications that affect the strength of contractions

Fast action potential (cont.)

- Phase 3
  - Marked by the cessation of calcium influx and rapid efflux of K+

Fast action potential (cont.)

- Phase 4
  - Normally a flat stage representing the resting membrane potential.
  - In Pathologic states, a slow influx of Na+ that will gradually make the cell more positive.

Fast action potential (cont.)

- Phase 4
  - When the interior of the cell reaches its threshold potential, the cell will depolarize without waiting for an impulse.
  - Many antidysrythmics have their mechanism of action during this phase

Slow action potential

- Located in the dominant pacemakers of the heart.
- Caused by a gradual influx of calcium in the cell

Slow action potential (cont.)

- Slow potentials undergo a gradual, phase 4 depolarization.
  - Responsible for the spontaneous generation of impulses in the SA and AV nodes.
  - Because the SA node has a faster rate of depolarization, it is the dominant pacemaker.

Dysrhythmia Generation

- Ischemia
- Hypoxia
- Acidosis or alkalosis
- Electrolyte abnormalities
- Excessive catecholamine
- Autonomic influences
- Drug toxicity
- Scarred and diseased tissue

Dysrhythmias result from disturbances in impulse formation, conduction, or both

Most prevalent types of dysrhythmias

- Tachycardia
- Bradycardia

Usually caused by an imbalance between the sympathetic and parasympathetic nervous system stimulation

- Excessive **parasympathetic** stimulation causes **bradycardias**.
- **Tachycardias** have a **variety of causes** and are treated with antidysrhythmics

Antidysrhythmics

- Used to treat and prevent disorders of cardiac rhythm
- Work by a direct action on the cardiac cell membrane (lidocaine), by indirect action that affects the cell (propranolol), or both

Classifications

- Based on mode of action on cardiac muscle
- Drugs that belong to the same class do not necessarily produce identical actions
- All antidysrhythmics have some ability to suppress automaticity

Class I- Sodium Channel Blockers

- Class I drugs are subdivided into Classes I-A, I-B, I-C
  - Class I-A drugs decrease conduction velocity and prolong the electrical potential of cardiac tissue
    - Example: procainamide (Pronestyl)

Class I- Sodium Channel Blockers (cont.)

- Class I-B drugs increase or have no effect on conduction velocity
  - Increases the rate of repolarization and reduces automaticity in ventricular cells
    - Example: lidocaine (Xylocaine)

Class I- Sodium Channel Blockers (cont.)

- Class I-C drugs profoundly slow conduction and are indicated only for life-threatening ventricular dysrhythmias
  - Example: flecainide (Tambocor)
- Group I-C drugs are not administered in the prehospital setting

Class II- Beta Blockers

- Class II drugs are beta-blocking agents that reduce adrenergic stimulation of the heart
- Example: propranolol (Inderal)

Class III- Potassium Channel Blockers

- Class III drugs are anti-adrenergic agents that have a positive inotropic action (agonist-antagonist)
- Increases contractility
  - Unlike other antidysrhythmics, drugs in this group do not suppress automaticity and have no effect on conduction velocity

Class III- Potassium Channel Blockers (cont.)

- Thought to terminate dysrhythmias that result from reentry of block impulses
- Example: bretylium tosylate (Bretylol)

Class IV Calcium Channel Blockers

- Thought to work by blocking the inflow of calcium through the cell membranes of the cardiac and smooth muscle cells
- Depresses the myocardium and smooth muscle contraction

Class IV Calcium Channel Blockers (cont.)

- Decreases automaticity
- In some cases, decreases conduction velocity
- Example: verapamil (Isoptin), nifedipine (Procardia), diltiazem (Cardizem).

Miscellaneous Antidysrhythmics

Adenosine (Adenocard)

- Does not fit any of the previous categories.
- Has a very short half life (about 10 seconds)
- Acts on both potassium and calcium channels, increasing potassium efflux and inhibiting calcium influx.
- **Results in hyperpolarization that effectively slows the conduction of slow potentials**

Digoxin (Lanoxin)

- Is a paradoxical drug.
- Is an effective antidysrhythmic.
- A potent prodysrhythmic (Generator of dysrhythmias)
- Decreases the intrinsic firing rate of the SA node and decreases velocity of AV node

Digoxin (Lanoxin) (cont.)

- Side effects include Bradycardia, AV blocks and PVCs

Magnesium

- Drug of choice for Torsade de pointes and other refractory V-Tach.
- Mechanism of action not known but it may act on sodium or potassium channels or on NA+ K+ ATPase

Antihypertensives

- Hypertension affects approximately 50 million Americans and has been directly related to increased incidence of:
  - Stroke
  - Cerebral hemorrhage
  - Heart and renal failure
  - Coronary heart disease

The ideal antihypertensive drug should:

- Maintain blood pressure within normal limits for various body positions
- Maintain or improve blood flow without compromising tissue perfusion or blood supply to the brain
- Reduce the work load on the heart
- Have no undesirable side effects
- Permit long-term administration without intolerance

Drugs that control hypertension affect pre-load

Classifications

- Diuretics
- Beta blockers and antiadrenergic drugs
- Vasodilators
- Angiotensin-converting enzyme (ACE) inhibitors

Calcium channel blockers are being used to treat hypertension

Diuretics

- Fluid and/or electrolyte imbalance occurs with increased frequency in patients who take diuretics
- Drug of choice in treating patients with hypertension and congestive heart failure
- Result in a loss of excess salt and water from the body by renal excretion

Diuretics (cont.)

- The decrease in plasma and extracellular fluid volume (which decreases preload and stroke volume), plus a direct effect on arterioles, results in lowered blood pressure
- Causes an initial decline in cardiac output, followed by a decrease in peripheral vascular resistance, and a lowering of the blood pressure

Loop diuretics

- Powerful, short-acting agents that inhibit sodium and chloride reabsorption in the Loop of Henle
- Cause excessive loss of potassium and water and an increase in the excretion of sodium

Loop diuretics (cont.)

- Produce fewer side effects than most other antihypertensives
- Hypokalemia and profound dehydration can result from their use
- Prescribed to patients who have renal insufficiency or who cannot take other diuretics
- Example: furosemide (Lasix)

Thiazides

- Moderately effective in lowering blood pressure
- May be given concurrently with other antihypertensives to prevent retention of sodium and water
- Example: hydrochlorothiazide (Hydrodiuril)

Potassium-sparing agents

- Promote sodium and water loss without potassium loss
- Used to treat hypertensive patients who become hypokalemic with other diuretics
- Also used to treat some edematous states such as cirrhosis of the liver with ascites
- Example: spironolactone (Aldactone)

Combinations of diuretic agents may be prescribed to lower blood pressure

- Usually include hydrochlorothiazide (HCTZ)
- Example: Aldactazide (HCTZ and spironolactone

Sympathetic Blocking Agents

Beta-adrenergic Antagonist

- Used to treat cardiovascular disorders, including hypertension
- Work by decreasing cardiac output and inhibiting renin secretion from the kidneys (result in lower blood pressure)

Beta-adrenergic Antagonist (cont.)

- Compete with epinephrine for available beta-receptor sites
- Inhibiting tissue and organ response to beta stimulation

Beta1-blocking agents (cardioselective)

- Atenolol (Tenormin)
- Metoprolol (Lopressor)

Beta1- and Beta2-blocking agents (nonselective)

- Labetalol (Normodyne, Trandate)
- Propranolol (Inderal)

Adrenergic Inhibiting Agents

Adrenergic Inhibiting Agents

- Work by modifying the sympathetic nervous system and are effective antihypertensive drugs

- Sympathetic stimulation
  - Increases heart rate and force of myocardial contraction
  - Constricts arterioles and venules
  - Causes the release of renin from the kidneys
  - Blocking this stimulation can reduce blood pressure

- Centrally acting adrenergic inhibitors
  - Clonidine hydrochloride (Catapres)
  - Methyldopa (Aldomet)
- Peripheral adrenergic inhibitors
  - Guanethidine sulfate (Ismelin)
  - Reserpine (Sandril, Serpasil)

- Alpha1- and Alpha2-blocking agents
  - Prazosin hydrochloride (Minipress)
  - Phentolamine (Regitine)

Combined Alpha/Beta Antagonists

Act directly on the smooth muscle walls of the arterioles, veins, or both

- Lowering peripheral resistance and blood pressure
  - Stimulate the sympathetic nervous system and activate the baroreceptor reflexes
  - Leading to an increased heart rate, cardiac output, and renin release
  - Combined therapy is usually prescribed to inhibit the sympathetic response
  - Also useful in treating angina pectoris

Nitrates dilate veins and arteries

- Dilated veins lead to venous pooling and a decreased blood return to the heart
- Reducing left ventricular end-diastolic volume and pressure
- Decreases myocardial oxygen demand and chest pain associated with ischemia

Arteriolar Dilator Drugs

- Diazoxide (Hyperstat IV)
- Hydralazine hydrochloride (Apresoline)
- Minoxidil (Loniten)

Arteriolar and venous dilator drugs

- Sodium nitroprusside (Nipride, Nitropress)
- Nitrates and nitrites

Other Combined Alpha/Beta Antagonists

- Amyl nitrite inhalant
- Isosorbide dinitrate (Isordil, Sorbitrate)
- Nitroglycerin (Nitrostat and others)
- Nitroglycerin paste (Nitro-Bid)
- Intravenous Nitroglycerin
- Angiotension-Converting-Enzyme (ACE) inhibitor

Table 9-5

Receptor	Response to Stimulation	Location
Alpha 1 (α_1)	Constriction	Arterioles
	Constriction	Veins
	Mydriasis	Eye
	Ejaculation	Penis
Alpha 2 (α_2)	Presynaptic terminals inhibition*	
Beta 1 (β_1)	Increased heart rate	Heart
	Increased conductivity	
	Increased automaticity	
	Increased contractility	
	Renin release	Kidney
Beta 2 (β_2)	Bronchodilation	Lungs
	Dilation	Arterioles
	Inhibition of contractions	Uterus
	Tremors	Skeletal muscle
Dopaminergic	Vasodilation (increased blood flow)	Kidney

*Stimulation of α_2 adrenergic receptors inhibits the continued release of norepinephrine from the pre-synaptic terminal. It is a feedback mechanism that limits the adrenergic response at that synapse. These receptors have no other identified peripheral effects.

(ACE) Inhibitor Drugs- Angiotensin Converting Enzyme

- The renin-angiotensin-aldosterone system plays an important role in maintaining blood pressure
- A disturbance in this system can result in hypertension
- Kidney damage can result in an inability to regulate the release of renin, causing an elevated blood pressure

- Angiotensin II is a powerful vasoconstrictor
  - Raises blood pressure and causes the release of aldosterone
- Contributes to sodium and water retention
- **ACE inhibitors prevents the conversion of angiotensin I to angiotensin II**

- The renin-angiotensin-aldosterone system is suppressed, lowering blood pressure
- Examples:
  - Captopril (Capoten)
  - Enalapril (Vasotec)
  - Lisinopril (Prinivil)

Angiotensin II Receptor Antagonist

Angiotensin II Receptor Antagonist

- Recently developed classification.
- Acts on the rennin-angiotensin-aldosterone system.
- Achieves the same effects as the ACE inhibitors without the side effects of cough and angioedema

Calcium Channel Blocking Agents

Calcium Channel Blockers

- Reduce peripheral vascular resistance by inhibiting the contractility of vascular smooth muscle
- Dilate coronary vessels in the same manner

Calcium Channel Blockers

- Important in
  - Treating hypertension
  - Decreasing the oxygen requirements of the heart (through decreased afterload) and increasing oxygen supply by abolishing coronary artery spasm, thus relieving the cause of angina pectoris

Calcium Channel Blockers

- Examples:
  - Verapamil (Isoptin)
  - Nifedipine (Procardia)
  - Diltiazem (Cardizem)

Direct Vasodilators

Direct Vasodilators

- Two classes
  - Those that **dilate arterioles** and those that **dilate arterioles and veins**
- Those that dilate arterioles
  - Causes decreased peripheral vascular resistance or afterload.
  - Results in lower BP, increased cardiac output and reduced workload

- Those that dilates arterioles and veins.
  - Dilating the veins increases capacity and decreases pre-load.
  - Decreases both pre-load and cardiac output

- Examples:
  - Selective Arteriole dilators
    - Hydralizine (Apresoline) Proto-type drug.
    - Minoxidile (Rogain)
  - Non-Selective Dilators
    - Sodiuim nitroprusside (Nipride)

Ganglionic Blocking Agents

Ganglionic blocking agents

- Block sympathetic and parasympathetic ganglia
- Decrease peripheral resistance, cardiac output, and stroke volume
- Are considered to be less safe than other antihypertensive drugs (Are rarely used today)

Cardiac Glycosides

Cardiac Glycosides

- Naturally occurring plant substances that have characteristic actions on the heart.
- Contain a carbohydrate molecule (sugar)
- When combined with water, is converted into a sugar plus one or more active substances

Cardiac Glycosides

- May work by blocking ionic pumps in the cellular membrane
- Which indirectly increases the calcium concentration which increases contractility

Cardiac Glycosides

- Affect the heart in two ways:
  - They increase the force of contraction (positive inotropic effect)
  - They have a dual effect on the electrophysiological properties of the heart
    - Modest negative chronotropic effect, causing slight slowing
- A more profound negative dromotropic effect, decreasing conduction velocity

Cardiac Glycosides

- Digoxin (Lanoxin) is used to treat heart failure and to manage certain tachycardias
- Side Effects
  - Cardiac glycosides have a small TI
  - Side effects are common
  - Symptoms may be neurological, visual, gastrointestinal, cardiac, or psychiatric

Digoxin (Lanoxin)

- Are often vague and easily attributed to a viral illness
- Common side effects include:
  - Anorexia
  - Nausea and vomiting
  - Visual disturbances
  - Flashing lights
  - Altered color vision
  - Cardiac rhythm disturbances

Digoxin (Lanoxin)

- Toxic effects are dose related
- Dysrhythmias may include bradycardias, tachycardias, and ventricular fibrillation

Drugs that affect the blood

Blood Coagulation

- A process that results in the formation of a stable fibrin clot that entraps platelets, blood cells, and plasma
- Results in a blood clot or thrombus

- Arterial thrombi are commonly associated with
  - Atherosclerotic plaques
  - Hypertension
  - Turbulent blood flow that damages the endothelial lining of blood vessels

- Hyper-coagulable states:
  - The mechanism behind the increased incidence of DVT in women who take birth control pills
  - Responsible for many of the familial thrombotic disorder

Agents that Affect Blood Coagulation

Antiplatelet agents

- Interfere with platelet aggregation
- Patients who take antiplatelet or anticoagulant drugs at home are at increased risk for life-threatening hemorrhage from trauma
- Sometimes prescribed prophylactically for patients at risk for arterial clots and those who have suffered MIs or CVAs

Antiplatelet agents

- Also used to treat certain valvular heart diseases, valvular prosthesis, and various intracardiac shunts
- Common antiplatelet drugs
  - Aspirin
  - Sulfinpyrazone (Anturane)
  - Dipyridamole (Persantine)

Anticoagulant agents

- Designed to prevent intravascular thrombosis by decreasing blood coagulability
- Used to prevent postoperative thrombo-embolism and during hemodialysis
- Have no direct effect on a blood clot that is already formed or on ischemic tissue injured as a result of a thrombus

Anticoagulant agents

- Major side effect of therapy is hemorrhage
- Examples:
  - Warfarin (Coumadin)
  - Heparin (Liquaemin)

Thrombolytic agents

- The use of thrombolytics in the prehospital setting is being studied in several areas of the U.S.
- Dissolve drug clots after their formation by promoting the digestion of fibrin
- The treatment of choice for treating AMI in certain groups of patients

Thrombolytic agents

- The goal is to re-establish blood flow and prevent myocardial ischemia and tissue death
- Also used to treat acute pulmonary embolism, DVT, and peripheral arterial occlusion